REFERRAL SOURCE AS A PREDICTOR OF TREATMENT OUTCOME IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

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# DEDICATION

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# REFERRAL SOURCE AS A PREDICTOR OF TREATMENT OUTCOME IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

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REFERRAL SOURCE AS A PREDICTOR OF TREATMENT OUTCOME IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

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Information was obtained from two previously conducted studies of children and adolescents with major depressive disorder (Emslie et al., 2008; Kennard et al., 2008). Study participants were referred from advertisements, clinician or school counselors, and other sources. To date, two studies have examined referral source as a predictor of treatment outcome in youth with MDD, each yielding a different result. Thus, the purpose of the current study was to determine whether referral source is a predictor of treatment outcome in children and adolescents with major depressive disorder. Characteristics of acute study participants including age, gender, ethnicity, severity and duration of illness, suicidal behaviors, and number of comorbid diagnoses were compared between participants from differing referral sources. The findings of this study suggest that referral source is not a predictor of treatment outcome in children and adolescents with major depressive disorder.

TABLE OF CONTENTS

PAGE

LIST OF FIGURES

LIST OF TABLES

# CHAPTER ONE
## Introduction

## REFERRAL SOURCE AS A PREDICTOR OF TREATMENT OUTCOME IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) in children and adolescents is a serious disease due to its prevalence, morbidity and mortality (Kovacs, 1996). Children and adolescents often suffer tremendous impairment in social, familial, and academic functioning during a major depressive episode (Goodyer, Herbert, Secher & Pearson, 1997). Thus, the severe effects that may result from MDD highlight the need for significant clinical trials that may provide further insight into tailored treatments for depression.

In order for a clinical trial to be relevant however, the treatment must be modified for the target population. Therefore, moderators in the treatment of depression in children and adolescents have recently received more notice in the literature because they appear to be beneficial in treatment selection and planning (Emslie, Mayes, Laptook & Batt, 2003). Moderators are variables that are present before treatment and allow researchers to determine which participants are more likely to benefit from one of the studied treatments as compared to other treatments (Curry et al., 2006). Predictor variables are also helpful because they can be an indicator of general prognosis by indicating which participants are likely to benefit from any of the available treatments (Curry et al.). Several studies have shown that severity of illness, duration of illness, motivation level, and the presence of comorbid diagnoses are all viable predictors and moderators in the treatment of depression (Brent et al., 1998, Curry et al., 2006; Emslie et al., 2003; Goodyer et al., 1997). To our knowledge, however, only two studies to date have examined referral source as a treatment predictor in adolescent depression. Brent et al. (1998) found that

continued depression was predicted by referral source, partly mediated by hopelessness. Specifically, participants who entered the study via advertisement improved more than those referred by a clinician, which may have been due to their more positive attitude towards treatment. Contrastingly, the results from the Treatment for Adolescents with Depression Study (TADS) indicated that referral source was neither a predictor, nor a moderator, of treatment outcome (Curry et al., 2006).

A solid understanding of whether referral source (e.g. self-referred via advertisement, clinical/school referral, and other) predicts treatment outcome in children and adolescents with MDD is important because it may determine how future research studies stratify and examine their participants. If referral source is in fact a predictor of treatment outcome in children and adolescents with depression then it could indicate which study participants are likely to benefit from any of the provided treatments. Thus, if referral source predicts treatment outcome, then participants referred via different sources may appear clinically different from one another and require alternative treatments.

Utilizing data collected from two previously conducted studies, we investigated whether referral source is a predictor of treatment outcome in children and adolescents with MDD. We first examined the referral source for all 452 participants screened in both studies (331 participants from the study by Emslie et al. (2008) and 121 participants from the study by Kennard et al. (2008) to determine whether referral source predicted admission to the study. Then, we determined whether there were any differences in the baseline clinical characteristics of the 240 participants who entered the acute phase of the clinical trials (168 participants from Emslie et al. and 72 participants from Kennard et al.)

when stratified by referral source (self-referred via advertisement, clinician/school referred, and other). Since the referral source was unknown for five of the participants who entered the acute phase, they were not included in the analyses. Baseline characteristics that were examined include age, gender, ethnicity, illness severity, length of illness, number of comorbid illnesses, and suicidal behaviors. Finally, we determined whether acute treatment outcome (measured by the Children's Depression Scale- Revised (CDRS-R) and Clinical Global Impressions (CGI) Scale) was predicted by referral source.

# CHAPTER TWO
# Review of the Literature

## Major Depressive Disorder

Major Depressive Disorder (MDD) is a chronic disorder of considerable public health importance and thus requires effective and customized treatments. Approximately 2% of children and 4%-8% of adolescents experience a major depressive episode (Birmaher et al., 1996). While MDD in children occurs at approximately the same rate in girls and boys, the female-to-male ratio becomes 2:1 in adolescence (Birmaher et al.). Moreover, juvenile-onset depression tends to be more chronic than adult-onset depression and has a higher rate of recurrence (Kovacs, 1996). Approximately half of patients relapse within 1 to 2 years after treatment, and 70% relapse within 5 years after treatment (Birmaher et al.).

According to the American Psychiatric Association, for a child or adolescent to be diagnosed with MDD, he or she must experience at least two weeks of persistent change in mood evident by either depressed or irritable mood, and/or loss of interest and pleasure, plus five continual symptoms including: (a) insomnia or hypersomnia (sleep disturbance), (b) increased or decreased appetite, (c) weight change, (d) wishing to be dead, suicidal ideation or attempts, (e) fatigue or loss of energy, (f) psychomotor retardation (slowed thinking) or agitation, (g) decreased self-worth or excessive guilt, (h) diminished ability to think or concentrate (DSM-IV-TR, 2000). Although the clinical picture of early-onset MDD is similar to MDD in adults, there are some differences due to the physical, emotional, and cognitive changes that children and adolescents experience (Birmaher et al., 1996). Children with MDD generally display more

behavioral problems, symptoms of separation anxiety, phobias, somatic complaints, and temper tantrums than adolescents or adults with MDD (Birmaher et al., 1996). Symptoms such as melancholia, psychosis, suicide attempts, and impairment of functioning increase with age (Birmaher et al., 1996).

*Treatment of major depressive disorder*

Guidelines recommend specific psychotherapies, such as cognitive behavioral therapy (CBT) and Interpersonal Therapy (IPT), and/or antidepressant medications for treating MDD in youth (Birmaher, Brent & AACAP, 2007; Cheung et al., 2007). Since CBT and IPT are not easily accessible in every community, psychopharmacology is often the treatment of choice (Birmaher et al., 2007.). Antidepressants, particularly selective serotonin reuptake inhibitors (SSRI's), are frequently prescribed for moderately to severely depressed children and adolescents, or to those who have been unresponsive to psychotherapy (Sharp & Hellings, 2006). However, fluoxetine is currently the only SSRI that the FDA has approved for the treatment of depression in children 8 years and older (Birmaher et al., 2007). The SSRI citalopram was approved by the FDA in March 2009 for the treatment of MDD in adults and adolescents 12 to 17 years of age ("Forest Laboratories, Inc. Announces," 2009).

While the efficacy of medications in treating depression in youth remains a heavily debated topic, a meta-analysis of 13 trials and 2910 participants found that relative to placebo, antidepressants are effective treatments for MDD in adolescents (Bridge et al., 2007). Specifically, there have been three positive trials with fluoxetine in youth (Emslie et al., 1997, 2002; TADS Team, 2002). Additionally, Wagner et al. (2003) found that two randomized, placebo-controlled trials demonstrated that the antidepressant

sertraline was superior to placebo in the treatment of depression in children and adolescents as measured by the overall change in the CDRS-R. Wagner et al. (2004) also found that the SSRI citalopram was superior to placebo in a randomized trial of 174 children with MDD. In 2006, Wagner et al. conducted a randomized, controlled study of 264 children 6 to 17 years of age and found that escitalopram (the therapeutically active S-enantiomer of citalopram) was superior to placebo in treating adolescents with MDD. Similarly, Emslie, Ventura, Korotzer and Tourkodimitris (2009) found that escitalopram was effective in treating depressed adolescents.

*Moderators and Predictors of treatment outcome*

In order to select the most appropriate treatment for a child or adolescent with MDD, a clinician must first know for whom and under what conditions the treatment works (Kraemer et al., 2002). According to Kraemer et al., moderators aid researchers in deciding on treatment stratification and inclusion/exclusion criteria to use in clinical trials (2002). Thus, treatment moderators are valuable because they identify which youth are more likely to benefit from a particular treatment and can predict the level of impact a treatment will have on persons with specific characteristics (Curry et al., 2006; Kraemer et al.). Predictor variables have a main effect on outcome and thus assist in providing reasonable treatment expectations to participants (Curry et al.). Demographic variables, comorbid disorders, and severity of illness are commonly used moderators and predictors in psychiatry research to help explain individual differences in the effect of treatments or predict outcome (Curry et al.; Kraemer et al.).

*Definitions of mediators, predictors, and moderators*

To clarify the difference between a mediator, predictor, and moderator, Kraemer et al. provided detailed descriptions (2002). Mediators are variables that occur during treatment and may have a main or interactive effect on outcome (Kraemer et al.). A mediating variable serves to clarify or explain the relationship between the independent and dependent variable (Kraemer et al.). Contrastingly, both predictors and moderators are present before treatment and are uncorrelated with the treatment condition (Kraemer et al.). Predictors indicate "which adolescents are likely to benefit from any of the provided treatments and can be considered an indicator of general prognosis" (Curry et al., 2006, p. 1428). In comparison, "a moderator answers the question of which adolescents are more likely to benefit from one of the studied treatments as compared with the others and can be considered an indicator with prescriptive value" (Curry et al., p.1428).

*Referral source as predictor*

Clearly, there are many potential predictors in the treatment of childhood and adolescent depression, although studies have been inconsistent. Several studies of child and adolescent MDD have found age, duration and severity of illness, presence of comorbid diagnoses, and impairment level to be predictors of treatment outcome (Brent et al., 1998; Curry et al., 2006; Emslie et al., 2003; Goodyer et al., 1997; Jayson, Wood, Kroll, Fraser & Harrington, 1998; Vostanis, 1998). However, whether or not referral source is a predictor of treatment outcome remains unclear. In 1998, the hallmark CBT study by Brent and colleagues examined 107 adolescents ages 13 to 18 with a primary diagnosis of MDD who were recruited through clinical referrals, as well as radio and

print advertisements. The adolescents who met inclusion criteria were randomly assigned to one of three manual-based psychosocial treatments: cognitive-behavioral therapy (CBT), systemic-behavioral family therapy, or nondirective supportive therapy (Brent et al.). MDD at the end of treatment was predicted by comorbid anxiety disorder, high levels of cognitive distortion, hopelessness, and clinical referral (versus self-referred via advertisement) (Brent et al.). An important discovery from the analysis of the referral source was that participants in both groups (clinician referred and self-referred) had very similar demographic and clinical profiles. However, participants who came to the study via advertisement showed less hopelessness, and thus might have been less pessimistic about treatment (Brent et al.).

Contrary to these findings, the Treatment for Adolescents with Depression Study (TADS), did not find referral source to be a predictor or moderator of treatment outcome. The 439 participants, ages 12 to 17 years, were recruited at 13 clinical sites and randomly assigned to fluoxetine, CBT, fluoxetine and CBT, or pill placebo (Curry et al., 2006). TADS found age, severity of illness, number of comorbid illnesses, and suicidal behaviors to be predictors of treatment outcome. In other words, younger aged, higher functioning, less chronically depressed adolescents with less hopelessness responded more positively to treatment (Curry et al.). Thus, adolescents with shorter depressive episodes were likely to have benefited from acute intervention more than adolescents suffering with longer depressive episodes (Curry et al.). Additionally, the prognosis was better for adolescents with less suicidal ideation, fewer comorbid diagnoses, and greater expectations for improvement (Curry et al.). TADS also found that adolescents with higher level of severity did not significantly benefit from the addition of CBT to

fluoxetine (Curry et al.). The study did not find referral source, gender, ethic group or verbal intelligence to be predictors or moderators of outcome (Curry et al.).

May, Hallin, Kratochvil, Puumale, Smith and Reinecke et al. (2007) further reviewed the data from TADS to determine whether sex, age, race, or referral source was associated with eligibility, providing consent to treatment, or randomization. They found that 29.8% of the participants were professionally referred to the study, whereas 57.4% of the participants were recruited via advertisement (May et al.). The rest of the participants were recruited by other sources or by personal referral (May et al.). They also discovered that while race and source of recruitment did not predict the likelihood of being eligible to participate, adolescents referred by a health care provider were more likely to enter the study than those recruited by advertisement (May et al.).

One additional study in adults with anxiety and depression also suggests referral source may impact outcome. Participants who were either self-referred or referred by a general practitioner or a mental health professional, were treated with computer-aided cognitive-behavior therapy (CCBT) (Mataix-Cols, Carmeron, Gega, Kenwright & Marks, 2006) . The study results indicated that motivation for change was the highest in the self-referred group and lowest in the group referred by a mental health professional (Mataix-Cols et al.). Mataix-Cols et al. also found that participants who were self-referred or referred by a general practitioner were generally less severe and more likely to benefit from CCBT. Thus, the results suggest that different referral sources provide participants with differing levels of severity, motivation to change, and comorbidity; thus leading to varying treatment outcomes (Mataix-Cols et al.).

*Rationale for the current study*

Major depressive disorder in children and adolescents is a serious disorder that requires accurate and timely diagnoses, as well as modified treatments. Understanding the predictors in the treatment outcome for children and adolescents with depression may be very helpful in selecting appropriate treatments for youths with depression. However, the two studies that examined referral source as a treatment predictor in adolescent depression yielded contradicting results. Thus, the main goal of this study was to determine whether referral source (self-referral via advertisements, clinician/school referral, or other) is a predictor in the treatment outcome of children and adolescents with MDD. In order to determine whether clinical differences exist between the referral groups, several baseline characteristics such as age, gender, ethnicity, depression severity, duration of illness, and number of comorbid illnesses were compared between the participants who were referred by advertisements, a clinician or school personnel, and other source .

*Research Questions:*

1. Of the 452 participants screened, was referral source related to having a MDD diagnosis? Were the self-referred (via advertisement), clinician/school referred, or other participants more likely to enter acute treatment?
2. Are there differences in the baseline clinical characteristics (age, gender, ethnicity, depression severity, duration of episode, number of episodes, number of comorbid illnesses, and suicidal behaviors) between the 240 participants who entered acute treatment when stratified by referral source?
3. Is acute treatment outcome predicted by referral source?

# CHAPTER THREE
# Methodology

## Participants

This study utilized an overall sample of 452 children and adolescents evaluated for a primary diagnosis of major depressive disorder (MDD) at a general child and adolescent psychiatry outpatient clinic. The sample was derived from two previously conducted studies that both examined the effects of the antidepressant fluoxetine on children and adolescents who met DSM-IV criteria for MDD. Although the studies were conducted at different times, they both used the same inclusion and exclusion criteria. Emslie et al. (2008) evaluated 331 participants 7-18 years of age and 168 participants entered the acute phase of the trial where they were given 12 weeks of treatment with fluoxetine. The majority of participants were Caucasian (75%) and approximately 43% were female (Emslie et al.). Kennard et al. (2008) evaluated 121 participants 11-18 years of age and 72 participants entered the acute phase where they were given 12 weeks of fluoxetine. The majority of participants were Caucasian (74%) and approximately 48% were female (Kennard et al.).

### *Referral Source Categories*

In both studies, participants were recruited from advertisements, clinical and school referrals, and other sources (Emslie et al., 2008; Kennard et al., 2008). Clinician and school referrals were classified as one referral category after statistical analyses indicated that these groups were very similar across all tested dimensions. Additionally, many of the school referrals were from school counselors who are Licensed Professional Counselors just like some of the clinicians. Advertisement referrals included radio and

newspaper ads, flyers, and brochures. Participants referred via other sources included those who heard about the study from a friend, a participant in another study at UT Southwestern, a UT Southwestern employee, or by word of mouth.

*Inclusion and Exclusion Criteria*

Participants with comorbid disorders such as anxiety, attention deficit hyperactivity disorder (ADHD), and conduct disorder, were included in both studies (Emslie et al., 2008; Kennard et al., 2008). However, in order to qualify, participants must have had a primary diagnosis of MDD for at least four weeks (Emslie et al.; Kennard et al.). All participants in both studies were in good general health and of normal intelligence (Emslie et al.; Kennard et al). Exclusion criteria included: (a) a lifetime history of any psychotic disorder, (b) bipolar disorder, (c) anorexia nervosa, (d) bulimia, (e) alcohol or substance abuse within the previous 6 months, (f) severe suicidal ideation requiring inpatient treatment, (g) concurrent psychotropic medications (other than stable ADHD treatment), (h) concurrent medical condition that would endanger the participant, (i) pregnant or lactating females not using contraception, (j) first degree relatives with bipolar I disorder, (k) and previous failure with or intolerance to fluoxetine (Emslie et al.; Kennard et al.,). Participants who met inclusion criteria were enrolled in a 12 week open-label treatment study (Emslie et al.; Kennard et al.).

*Institutional Review Board*

To ensure that the clinical trials were ethical and the rights of the participants were protected, the trials were first approved by the University of Texas Southwestern Medical Center Institutional Review Board (Emslie et al., 2008; Kennard et al., 2008). Prior to the start of any study procedures, participants and their guardians were informed

of the purpose, risk and benefits of the study and all of their questions were answered (Emslie et al.; Kennard et al.). All participants and their guardians provided written informed consent and assent (Emslie et al.; Kennard et al.).

*Instrumentation*

The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime (K-SADS-PL) is a semi-structured interview that was administered to the participant and guardian separately (Kaufman et al., 1997). The information collected in both the participant and guardian interview was recorded on a common answer sheet and diagnoses were derived by synthesizing the data from both interviews (Kaufman et al.). The inter-rater reliability for the K-SADS-PL is high with 93% to 100% agreement in assigning present and lifetime diagnosis while the test-retest reliability for MDD is excellent with a reliability κ coefficient of .90 (Kaufman et al.). The concurrent validity is also well supported since children who meet criteria for current depressive disorders score significantly higher ($z = .21$) on the z score-transformed depression scale than children without MDD ($z = -.33$) (Kaufman et al.).

The Children's Depression Scale- Revised (CDRS-R; Pozanski & Mokros, 1996) is a clinician-administered rating scale that was used to measure the severity of depression in the participants (Emslie et al., 2008; Kennard et al., 2008). The clinician rates 17 symptom areas such as social withdrawal, impaired schoolwork, depressed feelings, irritability, physical complaints, excessive guilt, hypoactivity, excessive fatigue, and suicidal ideation (Poznanski & Mokros). Fourteen items are rated on a 7-point scale and three items are rated on a 5-point severity scale, allowing the CDRS-R to capture small but noticeable changes in symptoms (Mash & Barkley, 2007). The clinician ratings

result in total raw scores ranging from 17 to 113 and remission is defined as a CDRS-R score ≤ 28 (Pozanski & Mokros). The CDRS-R has good inter-rater reliability (r =.92), internal consistency (coefficient α = .85), and test-retest reliability (r = .78), while the correlation between CDRS-R scores and Global Rating Scale (.87) exhibits good convergent validity (Pozanski & Mokros).

The Clinical Global Impressions (CGI) Scale is a clinician-rated assessment tool frequently used in studies investigating the efficacy of pharmacological treatments for psychiatric conditions (Berk, Ng, Dodd, Callaly, Campbell, Bernardo & Trauer, 2008). The first subscale, designated as Severity of Illness (CGI-S), rates the severity of the patient's illness on the following seven-point scale: 1= normal, not at all ill; 2= borderline mentally ill; 3= mildly ill; 4= moderately ill; 5= markedly ill; 6= severely ill; 7= among the most extremely ill patients (Busner & Targum, 2007). The severity rating requires the clinician to rate the severity of the patient's illness at the time of assessment and is based on observed and reported symptoms, as well as the patient's behavior and level of functioning in the past seven days (Busner & Targum). The second subscale, designated as Global Improvement (CGI-I), is similar to the CGI-S in its format and is used each time the patient is seen after beginning medication (Busner & Targum). The clinician compares the patient's current condition to his or her condition prior to medication initiation using the following seven-point scale: 1= very much improved; 2= much improved; 3= minimally improved; 4= no change from baseline; 5= minimally worse; 6= much worse; 7= very much worse (Busner & Targum). Response is generally defined as a CGI-I of 1 or 2 (Busner & Targum).

In a study conducted by Dahlke et al. (1992), the test-retest reliability values for three clinical trials with 175 patients with depression, schizophrenia, or anxiety disorders ranged from 0.20 to 0.81 for CGI-S and 0.15 to 0.78 for CGI-I (as cited in Rush, First & Blacker, 2008). The study also found the Global Improvement and therapeutic effects scores were highly correlated ($r = 0.90$) (as cited in Rush et al.). Changes in the Severity of Illness subscale and the Global Improvement subscale were moderately correlated with ratings between -0.47 and -0.66 (as cited in Rush et al.).

*Procedure*

Children and adolescents referred to both of the studies were first screened by telephone and then scheduled for an initial diagnostic interview (Emslie et al., 2008; Kennard et al., 2008). Participants and their guardians were interviewed separately using the K-SADS-PL in order to obtain an estimated onset and duration (in weeks) of the participant's current major depressive episode, as well as the participant's total number of current comorbid diagnoses (Emslie et al.; Kennard et al.). The way in which the participant learned of the study (i.e. referral source) was also recorded. The interviewer used the Family Global Assessment Scale to acquire information about family functioning and the Family History Research Diagnostic Criteria to obtain a family psychiatric history (Emslie et al.; Kennard et al.). One week later, participants were evaluated by a psychiatrist or licensed psychologist using the K-SADS-PL, CDRS-R, and CGI-S to obtain information about the course and severity of illness (Emslie et al.; Kennard et al.). Participants with a primary diagnosis of MDD, who met all of the inclusion criteria and no exclusion criteria, and who had a CDRS-R score $\geq 40$ were scheduled to start acute treatment within 5-10 days (Emslie et al.; Kennard et al.).

To minimize threats in internal/external validity and generalizability, the participants were evaluated separately by an interviewer and then a psychiatrist, thus, requiring two different professional opinions before allowing admission to the study (Emslie et al; Kennard et al.). A child psychiatrist evaluated and completed all rating scales for every participant (Emslie et al.; Kennard et al.).

During the 12 week studies, participants received between 10-40mg of the antidepressant fluoxetine (Emslie et al., 2008; Kennard et al., 2008). The participants began open treatment with fluoxetine at the baseline visit (week 0), with an initial dose of 10mg per day for one week, after which the dosage was increased to 20mg per day (Emslie et al.; Kennard et al.). After six weeks of treatment, dosing could be increased to 30mg or 40mg if there was minimal or no response (i.e., CGI $\geq$ 3) (Emslie et al.; Kennard et al.). Fluoxetine could be reduced to 10mg if intolerable side effects were present (Emslie et al.; Kennard et al.). At each visit, the psychiatrist assessed each participant's depressive symptoms using the CDRS-R (Emslie et al.; Kennard et al.). The outcome measure for both of the studies was response to treatment or a CGI-I score of 1 (very much improved) or 2 (much improved) (Emslie et al.; Kennard et al.). The second outcome measure in both studies was remission or a CDRS-R score less than or equal to 28 (Emslie et al.; Kennard et al.).

*Statistical Analysis*

Statistical analyses were conducted using SPSS. Due to missing data for various measures, the sample sizes that were analyzed differed and are reflected in the different degrees of freedom in each analysis. One way analysis of variance (ANOVA) and chi-square procedures were used throughout to evaluate variable's potential influence on

outcome. Pearson's correlation coefficients were analyzed according to Cohen's (1988) effect sizes for *r* with small effects at .1, medium effects at .3, and large effects greater than .5. The level of significance for all tests was set at $p \leq .05$.

In the context of the previously reviewed questions, the following analyses were used:

1. Since we were able to determine the referral source for 430 of the 452 participants screened, we used chi-square procedures with a sample of 430 participants to determine whether referral source was related to eligibility for the study. Chi-square procedures were also used to determine how many of the 294 participants eligible for the study decided to enter acute treatment when stratified by referral source.
2. To determine whether any differences in the baseline characteristics exist between the participants who entered acute when stratified by referral source, chi-square procedures were conducted for gender and ethnicity. ANOVA procedures were used to examine the participants' average age, length and duration of episode, number of comorbid episode(s), severity of illness, and suicidal behaviors.
3. To determine whether acute treatment is moderated by referral source, ANOVA procedures were used to compare the average CDRS-R score change (from week 0 to week 12) between the three referral groups. To measure response, chi-square procedures were conducted to determine how many participants received a CGI-I score equal or less than two when stratified by referral source. To measure remission, chi-square procedures were conducted to determine how many participants had a CDRS-R score less than or equal to 28 when stratified by referral source.

# CHAPTER FOUR
# Results

## Association between Referral Source, MDD diagnosis, and Study Entry

A total sample of 430 participants was stratified by referral source and analyzed for whether or not they met DSM-IV criteria for MDD. Of the sample, 68.1% of the participants met criteria for MDD. No significant differences were found between the percent of participants who met criteria for MDD when stratified by referral source. Results of the analyses are presented in Table 1.

To determine whether referral source related to acute treatment entry, the number of participants who entered the study was stratified based on referral source. Table 2a and Figure 1 in Appendix A show the results of these analyses. Of the 430 participants analyzed, 235 (54.5%) entered treatment. There were no significant differences found between the participants who entered the study when stratified by referral source. However, the majority of the participants who entered treatment (67.6%) were referred via a clinician or school, while 25.5% were referred via advertisement and 6.9% were referred from other sources, which is consistent with the total screened sample. Figure 2 in Appendix A illustrates the results of these analyses. Of the participants referred via advertisement, 76.9% of those eligible to enter treatment decided to enter the study. Out of the participants referred via a clinician or school, 80.7% of those eligible decided to enter treatment, while 88.8% of the people referred from other sources decided to enter. Results of these analyses are presented in Table 2a.

### *Demographic Characteristics of Participants Stratified by Referral Source*

The total sample of 235 participants who entered the acute phase with a known referral source was analyzed for proportional breakdowns on the categorical variables of

gender and ethnicity. Additionally, the standard deviations and overall means were obtained for the continuous variable of age. Of the total sample, 55.7% of the participants were male and 44.3% were female. The mean age of the participants was 12.57 years (S.D. = 2.8), with a range from 7 to 18 years of age. The majority of the participants were Caucasian (76.2%) with the next largest group being Hispanic (12.3%). African-Americans made up 8.5% of the total sample, while 3% were classified as other ethnicities. Results of these analyses are presented in Table 3.

Pearson Chi-Square analyses were used to compare the three referral groups (advertisement, clinician/school, and other) on the categorical variables of race and ethnicity, while a one-way analysis of variance (ANOVA) was used to compare the three groups on the variable of age. No significant differences were found among the groups on the variables of age, gender, or ethnicity. Results of these analyses are presented in Table 3.

*Baseline Clinical Characteristics of Participants Stratified by Referral Source*

A one-way analysis of variance (ANOVA) was used to compare the baseline clinical characteristics between the three referral groups. No significant differences were found between the referral groups' CDRS-R total score at screening. The mean CDRS-R score of the 235 participants who entered the acute phase of the trial was 57.97 (S.D. = 8.1) with a score range from 40-88. Results of these analyses are presented in Table 4.

There were no significant differences between the CGI-S scores at screening or exit among the three referral groups. The results of these analyses are presented in Table 5 and Table 6. There were also no significant differences in the suicidal behavior at

screening between the three referral groups. The results of the analysis are presented in Table 7.

Statistically significant differences were found between the three referral groups' current episode length. For the participants referred via advertisement, the average current episode length was 33.8 weeks (S.D. = 29.8) with a range of 6 to 152 weeks. The participants referred via a clinician or school source had a current episode length of 23.7 weeks (S.D. = 19) with a range of 4 to 120 weeks. For the participants referred from other sources, the average current episode length was 21.2 weeks (S.D. = 15.3) with a range of 4 to 56 weeks. A post hoc analysis was run to determine where the differences were among the three referral groups. It revealed a difference between the participants referred via advertisement and those referred via a clinician or school at $p<.01$. The results also revealed a difference between the participants referred via advertisement and those referred from other sources at $p<.05$. Results of these analyses are presented in Table 4.

No significant differences were found among the referral groups when examining the number of MDD episodes the child or adolescent has experienced. The mean number of MDD episodes for the 235 participants who entered the acute phase was 1.39 (S.D. = .65). When comparing the average number of comorbid diagnoses between the groups, no significant differences were found. The mean number of comorbid diagnoses for all of the participants in the acute phase of the trial was 2.08 (S.D. = .91). Results of these analyses are presented in Table 4.

*Acute Treatment Outcome measured by the CDRS and CGI-I*

A one-way analysis of variance (ANOVA) was used to compare the CDRS-R scores at acute exit between the three referral groups. The results of the analysis showed

no significant differences between the CDRS-R scores at acute exit or the change in CDRS-R scores between the referral groups. The average CDRS-R score change (from week 0 to week 12) for the 235 participants was -29 (S.D. = 12.1). Pearson chi-square analyses were used to determine the percentage of participants with a CDRS-R score less than or equal to 28 at week 12 when stratified by referral source. The results of the analysis showed no significant differences between the referral groups on this measure. Of the total sample, 61.1% of the participants had a CDRS-R score equal to or less than 28 at week 12 which indicated remission. Pearson chi-square analyses were also used to determine the percentage of participants with a CDRS-R score decrease greater than 50% from week 0 to week 12. The results of the analysis did not indicate any significant differences between the referral groups. Of 188 participants evaluated on this measure, 80% had a CDRS-R score decrease of 50% or more. The results are presented in Table 8.

In order to measure response, chi-square procedures were utilized to determine the percentage of participants who has a CGI-I score equal to or less than 2 at week 12. The results of the analysis showed no significant differences when the participants were stratified by referral source. For the 182 participants evaluated on this measure, 77.8% had a CGI score equal to or less than 2.The results for these analyses are presented in Table 8.

## CHAPTER FIVE
## Discussion

The current study did not find referral source to be associated with whether participants met the DSM-IV criteria for MDD. If an adolescent did not meet diagnostic criteria for MDD, then no further screening procedures were required. Thus, we did not examine whether clinical differences existed between eligible and ineligible adolescents.

Although referral source was not found to be a statistically significant determinant of which participants entered acute treatment; analyses did reveal that a higher percentage of participants referred via a clinician or by a school entered the study than those referred via advertisements or other sources. However, the distribution rates were similar to the referral distribution for those evaluated for the study.

No significant differences were found among the referral groups on the variables of gender, ethnicity, or age. Correspondingly, Brent et al. (1998) found that participants referred via advertisements and those referred from a clinician both had similar demographic profiles. The current study did not find statistically significant differences between the referral groups' CDRS-R or CGI-S scores at screening. In other words, the referral groups did not differ in the levels of illness severity as measured by the CDRS-R or CGI-S. The results contradict earlier findings by Mataix-Cols et al. (2006) who determined that participants who were self-referred or referred by a general practitioner were generally less severe.

Statistically significant differences were found between the referral groups' current episode length. Participants referred via advertisement had a much longer average episode length (33.8 weeks) than participants referred via a clinician or school (23.7 weeks). The reason for this could be that those referred by a clinician or school are seen

regularly by a professional who may have noticed symptoms of MDD sooner and thus referred them to the study. Similarly, the average current episode length for participants referred from other sources (e.g. friend, another study patient, or word of mouth) was shorter than for those referred via advertisement.

The current study did not find any significant differences among the referral groups when examining the number of comorbid diagnoses or number of MDD episodes the participant has previously experienced (including the current episode). This finding was surprising given the fact that many participants referred via a clinician have been under the guidance of a physician or psychiatrist and thus may have had previous treatment for MDD episode or any comorbid illnesses.

The acute treatment outcome for participants did not appear to differ significantly between referral groups. Similarly to TADS, the results of this study indicated that referral source was not a predictor of treatment outcome. Acute treatment outcome was measured by the change in CDRS-R scores from screening (week 0) to acute exit (week 12) and the analyses did not show any significant differences between the referral groups. Treatment outcome was also measured by remission (CDRS-R $\leq$ 28 at week 12) and response (CDRS-R $\geq$ 50% decrease or CGI-I $\leq$ 2). Analyses indicated that remission and response was not significantly different among the referral groups.

*Clinical Implications*

The results of this study did not find referral source to be a predictor of treatment outcome. The only statistically significant result found was that the participants referred via advertisements had a longer current MDD episode length than those referred by a clinician/school or by another source. The reason for this could be that these participants

had been struggling with MDD for so long that their parent's decided to respond to an advertisement for a clinical trial on depression. Since all of the participants appeared to have similar demographic and clinical profiles regardless of referral source, it is most likely not necessary to study these participants separately.

*Study Limitations*

The data utilized in the current study was collected in two different studies that were open, uncontrolled trials. Since there was no randomization, clinician biases could have occurred. Although all the measures used were standardized, there may have been threats to internal and external validity. Since the studies were open and the patient's success was dependent on their ability to continue in the trial, clinicians may have been unconsciously biased towards viewing their patients as more improved than they really were. Also, because the treatment took place in a research setting, the patients were evaluated and seen by psychiatrists more frequently than in clinical settings. Thus, the greater amount of treatment and care may have limited the generalizability of the results.

Since the current study was not originally designed to investigate referral source, important limitations should be considered in interpreting our findings. Due to some inconsistent reporting of recruitment methods, we had to interpret clinical notes to determine the referral source for several of the participants. In many instances, specific information regarding the types of advertisement (radio ad, flyer, or brochure) was not collected. Additionally, some participants were given information about the research study when they called the Children's Medical Center outpatient clinic prior to actually seeing a psychiatrist. We included the participants that called Children's Medical Center as clinical referrals, but, in fact, we don't how they were referred to Children's, although

they were definitely not referred from an advertisement specifically for the depression study.

Although the sample size in the current study was respectable, the size of the referral groups was unevenly proportioned. The referral group labeled “other” that included word of mouth and friend referrals was much smaller than the other two groups. Therefore, there could have been different ways of classifying the referral groups that could have yielded differing results. Additionally, while the methodologies for the two studies were the same, the studies were conducted at different times with much different sample sizes. Thus, it is possible that there were some differences between the studies that we did not recognize during preliminary analyses. Finally, there may be ways that the referral groups differed that could not be detected by the information that we have. For example, the referral groups may differ in respect to family history or SES which were not analyzed in this study.

*Final Conclusions*

Although we did not find statistical differences between the referral groups, there were differences in the number of participants referred from each referral category. For example, 61.5 % of the overall sample screened came from clinician and school referrals. Contrastingly, 27.4% of the overall sample was referred from advertisements. Therefore, referral source could be an important consideration in research planning and funding. However, in order to most accurately determine the role that referral source plays in treatment outcome, it would be necessary to consistently report and collect referral source during the screening process of a study. Ideally, the family and participants would be

asked how they learned about the study and a specific referral category would be recorded along with a detailed description.

## Figures

Figure 1.

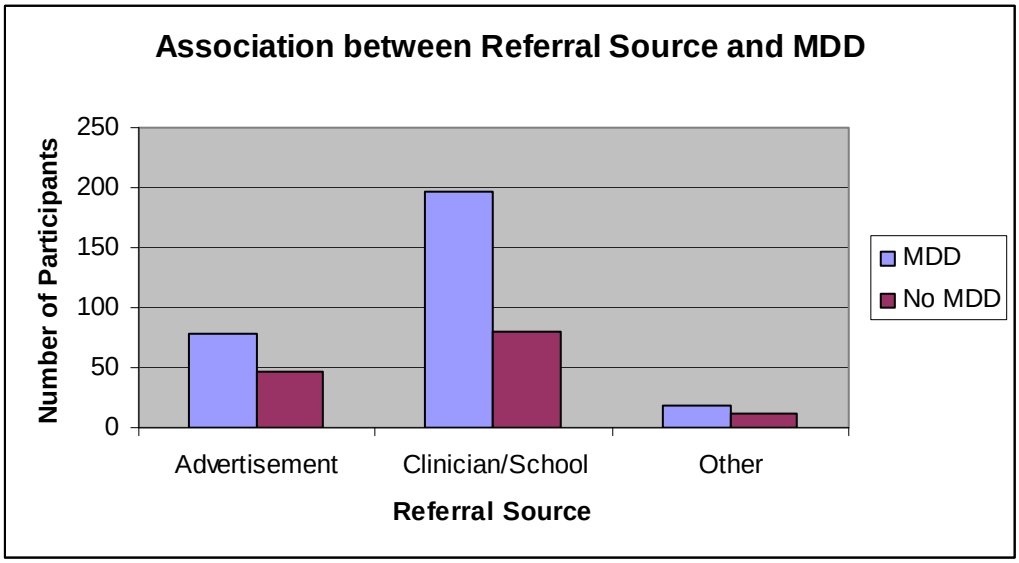
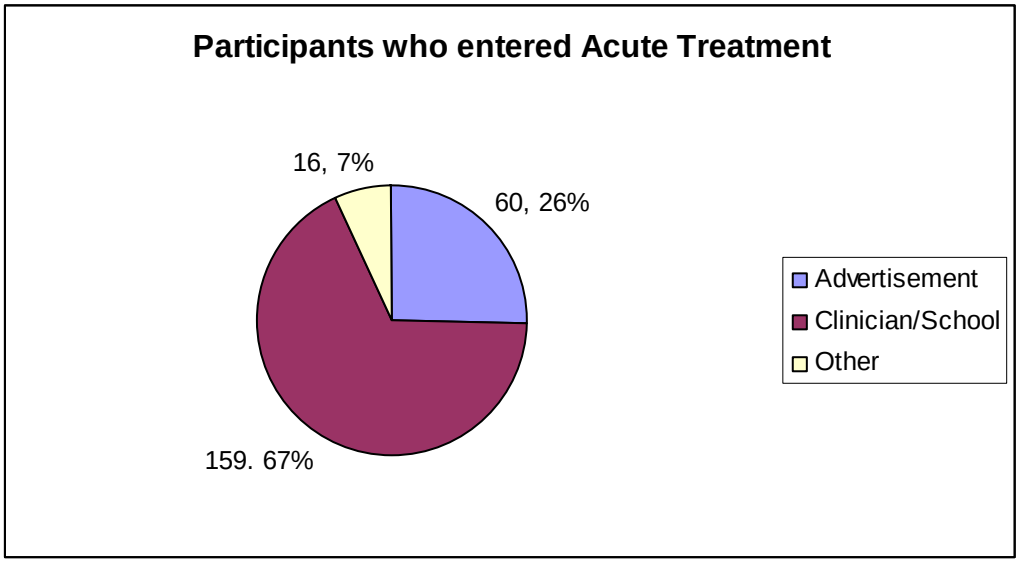


Figure 2.


Participants who entered Acute Treatment
16, 7%
60, 26%
159. 67%
Advertisement
Clinician/School
Other

## Tables

Table 1
Association between Referral Source and MDD diagnosis

| Diagnosis | Advertisement | Clinician/School | Other | Total |
|---|---|---|---|---|
| MDD, % (*n*) | 62.9 (78) | 71.1 (197) | 62.1 (18) | 68.1 (293) |
| No MDD, % (*n*) | 37.1 (46) | 28.9 (80) | 37.9 (11) | 31.9 (137) |
| Total | 100 (124) | 100 (277) | 100 (29) | 100 (430) |

Table 2a
Association between Referral Source and Entering the Study

| Enter Study | Advertisement | Clinician/School | Other | Total |
|---|---|---|---|---|
| Yes, % (*n*) | 48.4 (60) | 57.2 (159) | 55.2 (16) | 54.5 (235) |
| No, % (*n*) | 51.6 (64) | 42.8 (119) | 44.8 (13) | 45.5 (196) |

Table 2b
Association between Eligibility and Entry into the Study

| Enter Study | Advertisement | Clinician/School | Other | Total |
|---|---|---|---|---|
| Yes, % (*n*) | 76.9 (60) | 80.7 (159) | 88.8 (16) | 80.2 (235) |
| No, % (*n*) | 23.1 (18) | 19.3 (38) | 11.1 (2) | 24.6 (58) |

Table 3
Demographic Characteristics of Participants Stratified by Referral Source

| Characteristics | Advertisement | Clinician/School | Other | Total |
|---|---|---|---|---|
| Age, mean ± SD | 12.58 ± 2.8 | 12.52 ± 2.9 | 13.12 ± 2.6 | 12.57 ± 2.8 |
| Sex, % (*n*) | | | | |
| Male | 51.7 (31) | 58.5 (93) | 43.8 (7) | 55.7 (131) |
| Female | 48.3 (29) | 41.5 (66) | 56.2 (9) | 44.3 (104) |
| Ethnicity, % (*n*) | | | | |
| African American | 10 (6) | 8.8 (14) | 0 (0) | 8.5 (20) |
| Caucasian | 80 (48) | 74.2 (118) | 81.2 (13) | 76.2 (179) |
| Hispanic | 10 (6) | 13.2 (21) | 12.5 (2) | 12.3 (29) |
| Other | 0 (0) | 3.8 (6) | 6.2 (1) | 3 (7) |

Table 4
Baseline Clinical Characteristics of Participants Stratified by Referral Source

| Characteristics | Advertisement ($n$ = 60) | Clinician/School ($n$ = 159) | Other ($n$ = 16) | Total ($n$ = 235) |
|---|---|---|---|---|
| CDRS-R total at screening, mean ± SD (score range) | 58.87 ± 8.5 (46-88) | 57.43 ± 7.5 (42-84) | 60.06 ± 11.4 (40-83) | 57.97 ± 8.1 (40-88) |
| Current episode length (weeks), mean ± SD[a] (range in weeks) | 33.8 ± 29.8[1] (6-152) | 23.7 ± 19[1] (4-120) | 21.2 ± 15.3[2] (4-56) | 26.1 ± 22.4 (4-152) |
| No. of episodes, mean ± SD (range) | 1.28 ± .52 (1-3) | 1.41 ± .69 (1-4) | 1.56 ± .51 (1-2) | 1.39 ± .65 (1-4) |
| No. of comorbid diagnoses, mean ± SD | 2.23 ± .87 | 2.03 ± .94 | 2.12 ± .72 | 2.08 ± .91 |

[a] Three missing scores
[1] $p<.01$
[2] $p<.05$

Table 5
CGI Severity at Baseline Stratified by Referral Source

| Severity | Advertisement (*n* = 60) | Clinician/School (*n* = 158) | Other (*n* = 16) | Total (*n* = 234) |
|---|---|---|---|---|
| Moderately ill, % (*n*) | 25 (15) | 30.4 (48) | 31.2 (5) | 29.1 (68) |
| Markedly ill, % (*n*) | 58.3 (35) | 55.1 (87) | 37.5 (6) | 54.7 (128) |
| Severely ill, % (*n*) | 13.3 (8) | 14.6 (23) | 31.2 (5) | 15.4 (36) |
| Among the most ill, % (*n*) | 3.3 (2) | 0 (0) | 0 (0) | 0.9 (2) |

Table 6
CGI Severity at Acute Exit Stratified by Referral Source

| Severity | Advertisement (*n* = 60) | Clinician/School (*n* = 158) | Other (*n* = 16) | Total (*n* = 234) |
|---|---|---|---|---|
| Not at all ill, % (*n*) | 23.3 (14) | 19 (30) | 12.5 (2) | 19.7 (46) |
| Borderline ill, % (*n*) | 48.3 (29) | 39.2 (62) | 62.5 (10) | 43.2 (101) |
| Mildly ill, % (*n*) | 10 (6) | 24.1 (38) | 18.8 (3) | 20.1 (47) |
| Moderately ill, % (*n*) | 10 (6) | 13.3 (21) | 6.2 (1) | 12 (28) |
| Markedly ill, % (*n*) | 5 (3) | 3.2 (5) | 0 (0) | 3.4 (8) |
| Severely ill, % (*n*) | 1.7 (1) | 1.3 (2) | 0 (0) | 1.3 (3) |
| Among the most ill, % (*n*) | 1.7 (1) | 0 (0) | 0 (0) | 0.4 (1) |

Table 7
Suicidal Behavior at Baseline

| Severity | Advertisement (*n* = 59) | Clinician/School (*n* = 157) | Other (*n* = 16) | Total (*n* = 232) |
|---|---|---|---|---|
| None, % (*n*) | 20.3 (12) | 19.7 (31) | 29.4 (5) | 20.6 (48) |
| Morbid Ideation, % (*n*) | 44.1 (26) | 31.2 (49) | 23.5 (4) | 33.9 (79) |
| Suicidal Thoughts, % (*n*) | 20.3 (12) | 38.9 (61) | 29.4 (4) | 33.5 (77) |
| Suicidal Plans, % (*n*) | 6.8 (4) | 8.3 (13) | 11.8 (2) | 8.2 (19) |
| Suicidal Attempts, % (*n*) | 8.5 (5) | 1.9 (3) | 5.9 (1) | 3.9 (9) |

Table 8
Acute Treatment Outcome measured by the CDRS-R and CGI-I at Acute Exit (week 12)

| Characteristics | Advertisement (*n* = 60) | Clinician/School (*n* = 159) | Other (*n* = 16) | Total (*n* = 235) |
|---|---|---|---|---|
| CDRS-R total at week 12[a], mean ± SD (range) | 28.78 ± 12.5 (17-82) | 29 ± 10.1 (17-57) | 27.1 ± 6.4 (20-44) | 28.8 ± 10.6 (17-82) |
| CDRS change[b], mean ± SD | -30.08 ± 11.9 | -28.3 ± 12.1 | -32.88 ± 12.2 | -29 ± 12.1 |
| CDRS ≤ 28 at week 12, % (*n*) | 66.7 (40) | 58.9 (93) | 62.5 (10) | 61.1 (143) |
| CDRS ≥ 50% decrease, % (*n*) | 81.7 (49) | 78 (124) | 93.8 (15) | 80 (188) |
| CGI-I ≤ 2 at week 12, % (*n*) | 78.3 (47) | 76.6 (121) | 87.5 (14) | 77.8 (182) |

[a] One missing score due to early exit
[b] One missing score

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